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Patent- og Varemærkestyrelsen
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PATENT- OG VAREMÆRKESTYRELSEN

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MEDICAL DEVICE

Technical field

The present invention relates to a method of producing a medical device for insertion into the vascular system of a living being, in particular an intravascular stent or catheter. The invention also relates to such a medical device, and to a tubular member for temporary insertion into tubular structures of a living being for local treatment of cell disorders, its method of manufacture and various applications thereof.

Background of the invention

Medical devices, such as guide wires, medical tubings including catheters, or implants, including vascular implants, such as vascular grafts, stents, stent grafts, balloons and embolization devices are often used in various diagnostic procedures and medical treatments. Fluid drugs may for example be delivered into the vascular system of a living being by means of intravascular catheters. Stents for implantation in the lumen of a body duct are mainly used in the treatment of blood vessels exhibiting stenosis. Stents may contain drugs that after implantation elute to the surrounding tissue as to avoid side effects such as cell proliferation. It is generally desired that medical devices for insertion into the vascular system of a living being meet certain physical requirements. For example, the medical devices must be able to conform to an often tortuous passage to the treatment site while being sufficiently rigid to enable secure insertion. Furthermore, the surfaces of such medical devices should be hydrophilic and have a low surface friction in order to facilitate introduction. The surfaces may be coated with nitric oxide containing polymer matrix in order to ensure that the surfaces are hydrophilic. Such Nitric oxide releasing matrixes may also relax or prevent arterial spasm once the medical device is in place. Medical devices which are intended to release drugs once inserted into the vascular system of a living being are usually covered or coated with appropriate pharmaceutical compounds. Expandable stents are often placed on an angioplasty balloon catheter which, once in place, is inflated in order to cause the stent to expand. Alternatively, stents may be made from a material which has a recovery capacity such as a super elastic alloy, such as Nitinol, so that the stents may automatically expand, once in place. Such self expanding stents are often delivered by a telescopic tube arrangement where an outer member is removed e.g. by forced sliding over an inner member to which the stent is fixed prior to expansion.

In the prior art, various medical devices, including stents and catheters, as well as methods for their manufacture have been proposed. US patent No. 6,030,371 discloses a method for nonextrusion manufacturing of catheters that can be used to produce catheters. A polymer material in a particulate preform is applied in a layer over an outer surface of a core member. By applying the layer in a particulate preform, a composition of the polymer material can be varied continuously as it is being applied to provide a variable hardness over the length of the catheter. A fibrous reinforcement can be used having a constant or variable pitch and a constant or variable number of fibers and fiber types may be employed. US 6,030,371 further discloses the use of a plurality of mandrels placed side-by-side to form a multiple lumen tubing.

Various nictric oxide (NO) donor compounds, pharmaceutical compositions containing such nitric oxide donor compounds and polymeric compositions capable of releasing nitric oxide have also been proposed in the prior art. US patent No. 5,691,423 discloses a polymeric composition capable of releasing nitric oxide, and US 5,962,520 is concerned with a polymer capable of carrying and releasing a pharmaceutical compound. US 5,958,427 is directed to nitric oxide donor compounds and to pharmaceutical compositions for pulmonary hypertension and other indications, and US 6,147,068 discloses a composition of amine that was reacted with nitric oxide for delivering nitric oxide.

Summary of the invention

It is an object of the present invention to provide a new method for producing a medical device for insertion into the vascular system of a living being.

In a first aspect, the invention provides a method of producing a medical implant, such as a medical tubing, such as a vascular implant, a vascular graft, stent, stent graft, embolization device or catheter for insertion into the vascular system of a living being, the method comprising the step of forming at least a portion of the medical device by spinning of nanofibers, preferably electrospinning of such nanofibers, which consolidate to form the medical device, or at least said portion thereof. It has been found that such spinning of nanofibers may be more easily or accurately controlled than methods relying solely on spraying of polymers toward a core. This may ultimately confer the further advantage that medical devices may be made with smaller dimensions, such as smaller diameters than hitherto. The present invention allows for the manufacture of devices, in particular implants, such as stents, stent grafts, vascular grafts, embolization devices or catheters, with relatively low diameters which, in comparison to devices with larger diameters, facilitate introduction of medical devices into the vascular system of a living being and reduce side-effects which may occur as a consequence of the introduction of medical devices. The spinning of nanofibers

allows for the manufacture of integrated composite devices, in which two or more materials are interlocked on a molecular scale, in small dimensions while maintaining a sufficient mechanical stability. Cross-sectional dimensions as small as the dimension of approximately 2-5 molecules of the spun material may be achieved. The size of the molecules evidently depends from the source material used, the size of a polyurethane molecule being usually in the range of less than 3000 nanometers. It will thus be appreciated that medical devices, such as stents etc., may be manufactured with a much smaller diameter than hitherto, typical prior art stents having a diameter of order of magnitude 2 mm and larger.

It has also been found that medical devices produced by preferred embodiments of the method according to the invention have a low surface friction, and that medical devices may be produced which are well-suited as reservoirs to drugs, i.e. medical devices in which the electrospun portions thereof constitute reservoirs for holding drugs or constitutes a matrix polymer source where the drug is either blocked into the molecule chain or adheres to or surrounds the molecule chain. The devices disclosed herein may carry any appropriate drug, including but not limited to nitric oxide compositions and heparin.

It should be understood that the term electrospinning comprises a process wherein particles are applied onto a base element which is kept at a certain, preferably constant, electric potential, preferably a negative potential. The particles emerge from a source which is at another, preferably positive potential. The positive and negative potentials may e.g. be balanced with respect to the potential of a surrounding environment, i.e. a room in which the process is being performed. The potential of the base element with respect to the potential of the surrounding atmosphere may preferably be between -5 and -30 kV, and the positive potential of the source with respect to the potential of the surrounding atmosphere may preferably be between +5 and +30 kV, so that the potential difference between source and base element is between 10 and 60 kV.

Various polymer-based materials and composit matrixes hereof may form the nanofibers, including polymer solutions and polymer melts. Applicable polymers are: polyamid, including nylon, polyurethane, fluoropolymers, polyolefins, polyimides, acryl, and polyesters. Further, carbon may be used as a fiber-forming material.

In general, a low surface friction may be achieved by applying a hygroscopic material as a fiber forming material for the electrospinning process. Accordingly, once introduced into the vascular system, the hygroscopic electrospun material absorbs bodily fluid, resulting in a hydrophilic low-friction surface. A hygroscopic surface may for example be achieved with a polyurethane or acryl material.

The art of electrospinning of nanofibers has developed considerably in recent years. US patent No. 6,382,526 discloses a process and apparatus for the production of nanofibers, which process and apparatus are useful in the method according to the present invention, and US patent No. 6,520,425 discloses a nozzle for forming nanofibers. It should be understood that the processes and apparatuses of the aforementioned US patents may be applicable in the method according to the present invention, but that the scope of protection is not restricted to those processes and apparatuses.

Typically, the diameter of the nanofibers is in the range of 2 to 4000 nanometers, preferably 2 to 3000 nanometers.

The base element of the nanospinning process may consist essentially of a string or a helical coil element which is preferably made from metal or from a polymer, such as a biodegradable polymer, such as from polylactidacid. A helical coil element may define any curved trajectory in space. For example, it may form a helical spring form or a so-called three-dimensional sphere in which the coil element extends in an apparently random fashion to match a cavity at the application site in the body of the living being. In certain embodiments, a further coil or three-dimentional sphere may be wound around a first coil which has the form of a helical spring. Coil elements are often employed as embolization devices.

Alternatively, the base element may comprise one or more particles, preferably metal particles, such as tantal or tungsten particles, onto which filaments are applied by electrospinning. The particles may be provided on a film of a plastics material, or they may be coated with electrospun nanofibers in a fluid bed arrangement. The fluid bed may be arranged with an air stream at a negative potential with the source of electrospinning at a positive potential. Such particles provided with an electrospun filament may be injected into the body of a living being through a micro catheter, which also may be produced by electrospinning of nanofibers. Such particles to which there is applied an electronspun nano filament are often employed as embolization devices.

It has surprisingly been found that a fibrous surface or a thrombogenic material provided, e.g. on a coil member covered with nanospun fibers, may enhance formation of thrombus or embolization which is advantageous for curing arterial malfunctions in the vascular system .

The device, for example a tubing, such as a catheter, implant, graft, stent or stent graft, may be produced by the present invention may define a plurality of sections along its length. For example, the sections may have different properties, such as different hardness. Such different properties may be arrived at by employing different fiber-forming materials for different sections and/or by changing production parameters, such as voltage of electrodes in

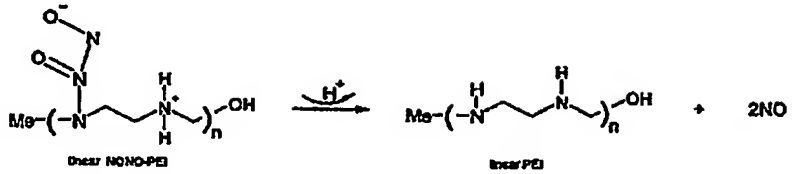
the electrospinning process, distance between high-voltage and low-voltage electrodes, rotational speed of the device (or of a core wire around which the device is manufactured), electrical field intensity, corona discharge initiation voltage or corona discharge current.

In a second aspect, the invention provides a tubular member for temporary insertion into tubular structures of a living being for local treatment of cell disorders, such as inflammation, proliferation and cancer, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance, wherein at least the outer surface layer is formed by nanofibers. Temporary insertion of the tubular member is usually applied in angioplasty, whereby a blood vessel is stretched and its cell tissue structure is traumatized. A risk of cell disorder during the healing of the blood vessel follows such angioplasty intervention and may lead to re-closure, i.e. blocking, of the blood vessel. Such re-closure may be prevented by the pharmaceutically active substance which is released to the cell tissue directly from the outer surface layer of the tubular element, while the tubular element is still in place at the treatment site. In one preferred embodiment, the outer surface layer is made from a nitric oxide donor compound, such as a nanofiber of linear poly(ethylenimine) diazeniumdiolate as disclosed in European patent No. EP 1 220 694 B1, which is hereby incorporated by reference in its entirety.

The body portion of the tubular member and the outer surface layer may be defined by one integrated polymer matrix, for example the molecule disclosed in EP 1 220 694 B1. It may be made from any suitable polyurethan and/or carbonate, and it may include a ph-decreasing compound, e.g. vitamin C, which acts as a catalyst for the NO release. Alternatively, the body portion of the tubular member and the outer surface layer may be defined by at least two separate polymer matrices. For example, the pharmaceutically active substance may be mixed into a liquid substance from which the body portion is manufactured prior to manufacturing of the body portion. In both alternatives, the outer surface layer may e.g. be manufactured by dip coating, co-extrusion or electrostatic spraying as described in more detail below. In summary, at least the polymer matrix of the outer surface layer may contain molecules capable of releasing the at least one pharmaceutically active substance.

The pharmaceutically active substance may comprise nitric oxide which is releasable in the gas phase, e.g. in order to prevent proliferation. It is desired that nitric oxide is released into the body tissue in the gas phase immediately upon placement of the tubular member at the treatment site, or within 5 minutes at most from its placement. As nitric oxide is released in the gas phase, it may be achieved that no or only few residues of the NO donor are deposited in the tissue.

In preferred embodiments of the present invention, NONO'ates may be applied as nitric oxide donors. NONO'ates break down into the parent amine and NO gas in an acid catalyzed manner, according to the below figure, cf. US 6147068, Larry K. Keefer: *Methods Enzymol*, (1996) **268**, 281-293, and Naunyn-Schmeidebergʼs *Arch Pharmacol* (1998) **358**, 113-122.



NO is released within the spun polymer matrix. As the matrix is porous, water may enter into the matrix. The NO molecule can be transported out of the matrix and into the tissue in a number of ways and combinations hereof. In the following some scenarios are described: NO becomes dissolved in water within the matrix and transported out of the matrix by diffusion or by water flow; NO diffuse out of the matrix in gas form and becomes dissolved in water outside the matrix; NO diffuses from water into the tissue; NO diffuses all the way from the matrix in gas form into the tissue.

As illustrated in the above figure, the rate of NO liberation highly depends on the pH of the media. Thus, by addition of various amounts of an acid to the matrix, the rate of NO liberation can be controlled. As an example, the half-live of NO liberation at pH = 5.0 is approximately 20 minutes whereas at pH = 7.4 the half-live is approximately 10 hours. As an example, the acid can be Ascorbic Acid.

The loading of NO onto the linear PEI can be varied. As an example, every third nitrogen within the linear PEI can be loaded with a NONO'ate moiety. Depending on the applied conditions the linear NONO-PEI can liberate various fractions of the total amount of releasable NO.

In order to facilitate passage of the tubular member to the treatment site along an often tortuous path, a hydrophilic layer is preferably applied to the outer surface layer. The hydrophilic layer may be provided as a separate layer of material. Alternatively, the outer surface layer may itself exhibit hydrophilic properties.

The outer surface layer may advantageously include vitamin C which acts as a catalyst for releasing the pharmaceutically active substance, e.g. nitric oxide. Vitamin C is capable of changing the ph-value at the treatment site, the release rate of nitric oxide at the treatment site varying as a function of the local ph-value. Thus, the presence of vitamin C may boost the nitric oxide release, i.e. provide a shock-like release of nitric oxide.

In general, the release of nitric oxide is described in *Prevention of intimal hyperplasia after angioplasty and/or stent insertion. Or, How to mend a broken heart* by Jan Harnek MD, Heart Radiology, University of Lund, Sweden, 2003.

Such shock-like release of vitamin C is in particular beneficial when the outer surface layer defines an outer surface layer of an angioplasty balloon. Thus, the body portion and the outer surface layer may define an expandable coated angioplasty balloon, such as a PTA (percutaneous translumenal angioplasty) balloon, a PTCA (percutaneous translumenal coronar angioplasty) balloon or a PTNA (percutaneous translumenal neurovascular angioplasty catheter).

The pharmaceutically active substance is provided in the form of biodegradable beadings distributed between the nanofibers, the beadings being capable of releasing the pharmaceutically active substance and, in the case of biodegradable beadings, to degrade following release. Such beadings, which are described in more detail in Danish patent application No. PA 2003 1204 corresponding to US provisional application No. 60/496,909 which is hereby incorporated by reference in its entirety, may penetrate into the tissue at the treatment site and release the pharmaceutically active substance there. Alternatively, the may be of a size which is so small that they may be transported away, e.g. with the flow of blood, away from the treatment site.

The nanofibers may be spun by electrospinning as described herein in connection with the first aspect of the invention. The diameter of the nanofibers is preferably in the range of 2 to 4000 nanometers.

The outer surface layer may be formed on a separate flexible tube or "sock" which is slipped over the tubular member. Accordingly, various flexible tubes having various properties or incorporating various pharmaceutically active substance may be inexpensively manufactured and slipped over traditional, mass manufactured balloons.

In an unexpanded state of the balloon, the flexible tube may be folded around the tubular member, so that the flexible tube, when seen in cross-section, defines a spoke-and-hub-formation with respect to the tubular member.

The outer surface layer may be formed by dip coating of said body portion or by dip coating of the flexible tube (or "sock"). Alternatively, the polymer matrices of the body portion and the outer surface layer are formed by co-extrusion, or, in yet another embodiment, the outer surface layer may be formed by electrostatic spraying of particles onto the body portion. These manufacturing processes are known *per se*. For example, dip coating is used in the rubber industry for the manufacture of latex products, and co-extrusion is e.g. applied in the manufacture of fibre-optics cables.

In case the tubular member is applied in the treatment of cancer, the pharmaceutically active substance may comprise a chemotherapeutical agent.

As described above, the pharmaceutically active substance may be contained in microparticles, such as microspheres and microcapsules. Such microparticles are in particular useful in the treatment of cancer. The microparticles may be biodegradable and may be made from a biodegradable polymer such as a polysaccharide, a polyamino acid, a

poly(phosphorester) biodegradable polymer, a polymers or copolymers of glycolic acid and lactic acid, a poly(dioxanone), a poly(trimethylene carbonate)copolymer, or a poly(α-caprolactone) homopolymer or copolymer.

Alternatively, the microparticles may be non-biodegradable, such as amorphous silica, carbon, a ceramic material, a metal, or a non-biodegradable polymer.

The microparticles may be in the form of microspheres that encapsulate the pharmaceutically active substance, such as the chemotherapeutic agent. The release of the pharmaceutically active substance commences after the administration.

The encapsulating microspheres may be rendered leaky for the pharmaceutically active substance by means of an electromagnetic or ultrasound shock wave.

In a third aspect, the invention provides a method of producing a tubular member for temporary insertion into tubular structures of a living being for local treatment of cell disorders, such as inflammation, proliferation or cancer, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance, wherein at least the outer surface layer is formed by nanofibers, the method comprising selecting at least one polymer matrix for the outer surface layer, which polymer matrix controls the rate of dilution of the pharmaceutically active substance. The tubular member may be a member according to the second aspect of the invention.

In a fourth aspect, the invention provides a method of treating cell disorders in tubular structures of a living being, comprising the steps of:
- placing a tubular member at a treatment site within the tubular structures, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance;
- expanding the tubular member at the treatment site;
- releasing the pharmaceutically active substance at the treatment site;
wherein the step of releasing is controlled by the presence of a ph-controlling substance contained in the outer surface layer.

The tubular member, which may be a tubular member according to the second aspect of the invention, may be self-expanding or balloon expanding.

In order to control the release of the pharmaceutically active substance as described above in connection with the second aspect of the invention, the ph-controlling substance may have a ph-decreasing effect at the treatment site, the ph-controlling substance comprising e.g. vitamin C.

The method according to the fourth aspect of the invention may e.g be applied in the treatment of cancer or stenosis.

Brief description of the drawings

A preferred embodiment of the invention will now be further described with reference to the drawing, in which:

Figs. 1-6 are step-by-step illustrations of a preferred embodiment of a method for producing a medical tubing;

Fig. 7 shows a longitudinal side view of the stent partially coated with nanospun fibers;

Fig. 8 illustrates an embolization device in the form of a three-dimensional sphere;

Fig. 9 is a cross-sectional illustration along line A-A in Fig. 8;

Fig. 10 illustrates an embolization device in the form of particle, onto which there is applied filaments by electrospinning;

Figs. 11-13 show two different embodiments of an angioplasty balloon catheter in accordance with the second aspect of the invention.

Detailed description of the drawing

Though the invention will now be further described with reference to the tubing illustrated in Figs. 1-6, the stent in Fig. 7 and the embolization devices of Figs. 8-10, it will be appreciated that the below description is not limited to medical tubing, stents and embolization devices. Accordingly, any other medical device for the introduction into the vascular system of a living being may be produced as described below.

In the embodiment of Figs. 1-6, the nanofibers are spun onto an outer surface of a core member. The core member comprises a core wire (or mandrel) 100, a layer 102 of PTFE applied to an outer surface of the core wire, a coating 104 of a thermoplastic material applied to an outer surface of the PTFE layer 102, and at least one reinforcing wire 106 applied to an outer surface of the thermoplastic coating, with the filaments of electrospun nanofibers being provided as an outer layer 108, i.e. enclosing the reinforcing wire and the thermoplastic coating. A hydrophilic layer 110 is optionally applied to an outer surface of the device, cf. Fig. 6.

Preferably, the diameter of the guide wire is at least 0.1 mm, preferably in the range of 0.1 to 1.0 mm. The thermoplastic coating, which is preferably a coating of polyurethane (PU), preferably has a thickness of 5 µm to about 0.05 mm, preferably 0.01 mm ±20%. The reinforcing wire(s) preferably has/have a diameter of 5 µm to about 0.05 mm, preferably 0.01 mm ±20%.

There may be provided one single core wire or a plurality of core wires which may be arranged side-by-side and extend in parallel. In the case of a plurality of core wires, the tubing so produced is a so-called multiple lumen tubing, with the core member being constituted by the plurality of core wires, around which the nanofibers are spun, so that the nanofibers and optionally the PTFE layer, thermoplastic layer and reinforcing wire(s) enclose the plurality of core wires. A multiple lumen tubing is for example useful in connection with pressure measurements, for example for measuring a pressure drop across stenosis. One or more passages of a multiple lumen tubing may be used for transmitting light, for example light which may be emitted through blood, thereby facilitating diagnostic procedures.

As described above, a layer of PTFE 102 may be applied to an outer surface of the core member 100. At least a portion of the surface of the layer of PTFE, such as the portion onto which the nanofibers and/or the thermoplastic coating are to be applied, may be modified for improved bonding of material to the outer surface of the PTFE layer. Preferably, such modifying comprises etching, which may for example result in a primed PTFE surface for covalent bonding or gluing. Etching may be achieved by applying a flux acid or hydrofluoric acid to a surface of the PTFE layer. The layer of PTFE may be provided as a hose which is slipped over and co-extends with the core wire, or, in the case of a multiple lumen tubing, the plurality of core wires.

A coating of a thermoplastic material 104, such as polyurethan (PU), may be provided to an outer surface of the core member 100, i.e. to an outer surface of the PTFE layer 102 in case such a layer has been provided. Following the step of providing the layer of PTFE 102 and/or the step of providing the thermoplastic coating 104, one or more reinforcing wires 106 may be applied to an outer surface of the core member 100, i.e., in a preferred embodiment, to an outer surface of the polyurethane coating 104. The reinforcing wire(s) may consist of one or wires made from steel or/and wires made from yarn, such as carbon filament, which may be applied by winding. Alternatively, the reinforcing wire may be applied by spinning of nanofibers, preferably by electrospinning as described above. The electrospun reinforcing wire may be formed from carbon or polymer, including polymer solutions and polymer melts. Applicable polymers are: nylon, fluoropolymers, polyolefins, polyimides, and polyesters.

While forming the medical device, or at least while forming that portion of the medical device which is formed by electrospinning, the core member 100 is preferably rotated, so as to evenly distribute the nanofibers around the outer surface of the core member.

In a preferred embodiment of the invention, nanofibers 108 are applied to the outer surface of the core member at this stage, that is preferably to the outer surface of the thermoplastic coating 104 which is optionally reinforced by the reinforcing wire(s). The electrospinning process is discussed in detail above.

A solvent, such as tetrahydroforane (THF) or isopropanol alcohol (IPA), may subsequently be applied to an outer surface of the core member, the outer surface being defined by the electrospun portion (or layer) 108 of the device. The thermoplastic coating 104 thereby at least partially dissolves in the solvent, so as to bond the reinforcing wire(s) 106 thereto. The reinforcing wire(s) 106 thereby become(s) embedded in the thermoplastic coating 104. It has been found that the step of providing the solvent results in a highly dense surface with a low surface friction, which is believed to be due to crumpling or shrinking of stretched molecules of electrospun nanofibers once the solvent is applied.

A stent graft may be produced by omitting the step of applying the solvent.

The core wire 100 (or mandrel) is removed from the device following the step of applying the solvent or prior to the step of applying solvent but subsequent to the step of applying the filament of electrospun nanofibers 108.

Fig. 7 illustrates a zig-zag corrugated stent 109 with portions of electrospun nanofilaments 111 applied to a surface thereof.

Fig. 8 illustrates an embolization device in the form of a three-dimensional sphere, produced by a method according to the invention. Electrospun nanofilaments are applied to a base element 112 which, as shown in the cross-section of Fig. 9, consists essentially of a string or coil element.

Fig. 10 illustrates an embolization device in the form of a tantal particle 114, onto which there is applied electrospun filaments 116.

Fig. 11 shows different embodiments of an angioplasty balloon catheter in accordance with the second aspect of the invention. In the upper drawing of Fig. 11 there is shown an inflated balloon which comprises an outer surface layer made from electrospun nanofibers. The balloon is carried by a guidewire 122.

The middle drawing of Fig. 11 shows a non-inflated balloon 124 over which there is slipped a tube or "sock" 126 made from electrospun nanofibers. In the lower drawing of Fig. 11m the dashed lines show the contour of the balloon 124 and the sock 126 when the balloon is inflated.

Figs. 12 and 13 are schematic illustrations of an unexpanded state of a balloon, wherein a flexible tube is folded around the tubular member, so that the flexible tube, when seen in cross-section, defines a spoke-and-hub-formation with respect to the tubular member.

CLAIMS

1. A method of producing a medical device for insertion into the vascular system of a living being, the method comprising the step of forming at least a portion of the medical device by spinning of nanofibers.

2. A method according to claim 1, wherein the step of spinning comprises electrospinning.

3. A method according to claim 1 or 2, wherein the diameter of the nanofibers is in the range of 2 to 4000 nanometers.

4. A method according to any of the preceding claims, wherein the step of spinning comprises feeding a first fiber-forming material into a nozzle for forming nanofibers by using a pressurized gas stream, and ejecting the first fiber-forming material from an exit orifice of the nozzle in the form of a plurality of strands of said first fiber-forming material that solidify and form said nanofibers.

5. A method according to any of the preceding claims, wherein the nanofibers are made from a polymer.

6. A method according to any of the preceding claims, comprising:
- providing at least one core member;
- forming the medical device by spinning the nanofibers onto an outer surface of the core member.

7. A method according to claim 6, wherein the step of providing the core member comprises providing a guide wire or a mandrel.

8. A method according to any of the preceding claims, wherein the diameter of the guide wire or mandrel is at least 0.1 mm.

9. A method according to claim 8, wherein the diameter of the guide wire or mandrel is at most 1.0 mm.

10. A method according to claim 6, wherein the step of providing the core member comprises providing a bundle of elongated members, so as to provide a multiple lumen tubing.

11. A method according to any of claims 6-10, further comprising, prior to the step of spinning, providing a layer of PTFE to an outer surface of the core member.

12. A method according to claim 11, further comprising modifying at least a portion of a surface of the layer of PTFE.

13. A method according to claim 12, wherein the step of modifying comprises etching.

14. A method according to any of the preceding claims, further comprising, prior to the step of spinning, providing a coating of a thermoplastic material to an outer surface portion of the core member.

15. A method according to claim 14, wherein the thermoplastic material is provided to an outer surface of the modified layer of PTFE.

16. A method according to claim 14 or 15, wherein the thermoplastic material consists essentially of polyurethane.

17. A method according to any of claims 6-16, further comprising applying, prior to the step of spinning, at least one reinforcing wire to an outer surface portion of the core member.

18. A method according to claim 17, wherein the at least one reinforcing wire is applied to an outer surface portion of the coating of said thermoplastic material.

19. A method according to claim 17 or 18, wherein the at least one reinforcing wire is applied by winding.

20. A method according to claim 19, wherein the reinforcing wire is made essentially from steel wire or yarn, such as carbon filament.

21. A method according to claim 17 or 18, wherein the at least one reinforcing wire is applied by spinning of reinforcing nanofibers.

22. A method according to claim 21, wherein the step of spinning said reinforcing nanofibers comprises electrospinning.

23. A method according to claim 21 or 22, wherein the diameter of the reinforcing nanofibers is in the range of 2 to 4000 nanometers.

24. A method according to any of claims 21-23, wherein the step of spinning said reinforcing nanofibers comprises feeding a second fiber-forming material into a nozzle for forming nanofibers by using a pressurized gas stream, and ejecting the second fiber-forming material from an exit orifice of the nozzle in the form of a plurality of strands of said second fiber-forming material that solidify and form said nanofibers.

25. A method according to any claims 21-24, wherein the reinforcing nanofibers are made from a polymer.

26. A method according to any of claims 7-25, further comprising removing the core wire or mandrel following the step of spinning said nanofibers.

27. A method according to any of claims 6-26, further comprising continuously rotating the core member while forming the medical device by spinning.

28. A method according to any of claims 17-27, further comprising applying a solvent to said outer surface portion of the core member, so as to bond the at least one reinforcing wire to the outer surface portion.

29. A method according to any of the preceding claims, wherein the solvent is applied subsequent to the step of forming said portion of the medical device by spinning of nanofibers.

30. A method of producing a medical stent assembly comprising an intravascular tubular stent, the method comprising producing the stent by a method according to any of the preceding claims.

31. A method of producing a medical catheter assembly comprising an intravascular tubular catheter, the method comprising producing the catheter by a method according to any of the preceding claims.

32. A medical device adapted to be inserted into the vascular system of a living being, at least a portion of the medical device being formed by spun nanofibers.

33. A medical device according to claim 32, wherein said portion is formed by elctrospun nanofibers.

34. A medical device according to claim 32 or 33, wherein the diameter of the nanofibers is in the range of 2 to 4000 nanometers.

35. A medical device according to any of claims 32-34, wherein the nanofibers are made from a polymer.

36. A medical device according to any of claims 32-35, the medical device enclosing a bundle of elongated members.

37. A medical device according to any of claims 32-36, wherein an inner layer of the medical device consists essentially of PTFE.

38. A medical device according to claim 37, wherein at least an outer surface portion of the PTFE layer has been modified.

39. A medical device according to claim 38, wherein outer surface portion of the PTFE layer has been modified by etching.

40. A medical device according to any of claims 32-39, wherein a coating of a thermoplastic material is provided to an outer surface portion of the PTFE layer.

41. A medical device according to claim 40, wherein the thermoplastic material is provided to an outer surface of the modified layer of PTFE.

42. A medical device according to claim 40 or 41, wherein the thermoplastic material consists essentially of polyurethane.

43. A medical device according to any of claims 40-42, wherein at least one reinforcing wire is applied to an outer surface portion of the coating of thermoplastic material.

44. A medical device according to claim 43, wherein the at least one reinforcing wire is made essentially from steel wire or yarn, such as carbon filament.

45. A medical device according to claim 43 or 44, wherein the at least one reinforcing wire is wound around said coating of thermoplastic material.

46. A medical device according to claim 43, wherein the at least one reinforcing wire is applied by spinning of reinforcing nanofibers.

47. A medical device according to claim 46, wherein the at least one reinforcing wire is applied by electrospinning of the reinforcing nanofibers.

48. A medical device according to claim 47, wherein the diameter of the reinforcing nanofibers is in the range of 2 to 4000 nanometers.

49. A medical device according to any of claims 46-49, wherein the reinforcing nanofibers are made from a polymer.

50. A stent assembly comprising an intravascular tubular stent, the tubular stent comprising a medical device according to any of claims 32-49.

51. A stent assembly according to claim 50, wherein the portion of the medical device which has been formed by spinning of nanofibers constitutes a reservoir to hold at least one drug.

52. A stent assembly according to claim 51, wherein said at least one drug is liquid-based.

53. A stent assembly according to claim 51 or 52, wherein said at least one drug comprises nitric oxide.

54. An intravascular medical catheter comprising a medical device according to any of claims 32-49.

55. An embolization device produced by a method according to any of claims 1-31.

56. A tubular member for temporary insertion into tubular structures of a living being for local treatment of cell disorders, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance, wherein at least the outer surface layer is formed by nanofibers.

57. A tubular member according to claim 56, wherein the body portion of the tubular member and the outer surface layer are defined by one integrated polymer matrix.

58. A tubular member according to claim 1, wherein the body portion of the tubular member and the outer surface layer are defined by at least two separate polymer matrices.

59. A tubular member according to any of claims 56-58, wherein at least the polymer matrix of the outer surface layer contains molecules capable of releasing the at least one pharmaceutically active substance.

60. A tubular member according to claim 59, wherein the pharmaceutically active substance is nitric oxide which is releasable in the gas phase.

61. A tubular member according to any of claims 56-60, wherein the outer surface layer is essentially made from a polymeric linear poly(ethylenimine) diazeniumdiolate.

62. A tubular member according to any of claims 56-61, wherein a hydrophilic layer is applied to the outer surface layer.

63. A tubular member according to any of claims 56-62, wherein at least the outer surface layer contains C-vitamin.

64. A tubular member according to any of claims 56-63, wherein the body portion and the outer surface layer define an expandable coated angioplasty balloon.

65. A tubular member according to any of claims 56-64, wherein the pharmaceutically active substance is provided in the form of biodegradable beadings distributed between the nanofibers.

66. A tubular member according to any of claims 56-65, wherein the nanofibers are spun by electrospinning.

67. A tubular member according to any of the claims 56-66, wherein the diameter of the nanofibers is in the range of 2 to 4000 nanometers.

68. A tubular member according to any of claims 56-67, wherein the outer surface layer is made from a hydrophilic material.

69. A tubular member according to any of claims 58-68, wherein the outer surface layer is formed on a separate flexible tube which is slipped over the tubular member.

70. A tubular member according to claim 69, wherein, in an unexpanded state of the balloon, the flexible tube is folded around the tubular member, so that the flexible tube, when seen in cross-section, defines a spoke-and-hub-formation with respect to the tubular member.

71. A tubular member according to any of claims 56-70, wherein the outer surface layer is formed by dip coating of said body portion.

72. A tubular member according to claim 69 or 70, wherein the outer surface layer is formed by dip coating of the flexible tube.

73. A tubular member according to any of claims 58-72, wherein the polymer matrices of the body portion and the outer surface layer are formed by co-extrusion.

74. A tubular member according to any of claims 56-68, wherein the outer surface layer is formed by electrostatic spraying of particles onto the body portion.

75. A tubular member according to any of claims 56-74, wherein the pharmaceutically active substance comprises nitric oxide.

76. A tubular member according to any of claims 56-75, wherein the pharmaceutically active substance comprises a chemotherapeutical agent.

77. A tubular member according to any of claims 65-76, wherein the pharmaceutically active substance is contained in microparticles.

78. A tubular member according to claim 77, wherein the microparticles are selected from microspheres and microcapsules.

79. A tubular member according to claim 78, wherein the microparticles are biodegradable.

80. A tubular member according claim 79, wherein the microparticles are of a material selected from the group consisting of a biodegradable polymer such as a polysaccharide, a polyamino acid, a poly(phosphorester) biodegradable polymer, a polymers or copolymers of glycolic acid and lactic acid, a poly(dioxanone), a poly(trimethylene carbonate)copolymer, and a poly(α-caprolactone) homopolymer or copolymer.

81. A tubular member according to claim 77 or 78, wherein the microparticles are non-biodegradable.

82. A tubular member according to claim 81, wherein the microparticles are of a material selected from the group consisting of amorphous silica, carbon, a ceramic material, a metal, and a non-biodegradable polymer.

83. A tubular member according to claim 82, wherein the microparticles are in the form of microspheres that encapsulate the pharmaceutically active substance and wherein release of the pharmaceutically active substance commences after the administration.

84. A tubular member according to claim 83, wherein the encapsulating microspheres are rendered leaky for the pharmaceutically active substance by means of an electromagnetic or ultrasound shock wave.

85. A method of producing a tubular member for temporary insertion into tubular structures of a living being for local treatment of cell disorders, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance, wherein at least the outer surface layer is formed by nanofibers, the method comprising selecting at least one polymer matrix for the outer surface layer, which polymer matrix controls the rate of dilution of the pharmaceutically active substance.

86. A method of treating cell disorders in tubular structures of a living being, comprising the steps of:
- placing a tubular member at a treatment site within the tubular structures, the tubular member defining a body portion and comprising an outer surface layer containing at least one pharmaceutically active substance;
- expanding the tubular member at the treatment site [self-expanding or balloon expanding];
- releasing the pharmaceutically active substance at the treatment site;
wherein the step of releasing is controlled by the presence of a ph-controlling substance contained in the outer surface layer.

87. A method according to claim 86, wherein the ph-controlling substance has a ph-decreasing effect at the treatment site.

88. A method according to claim 87, wherein the ph-controlling substance comprises vitamin C.

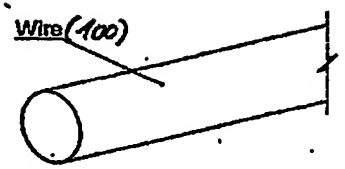


Fig. 1

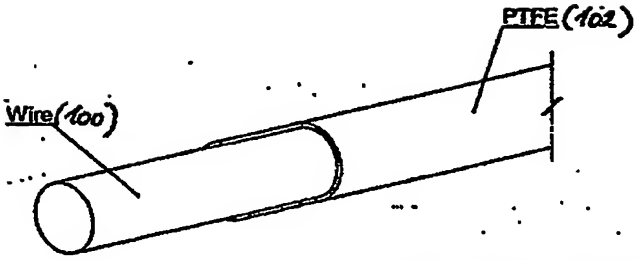


Fig. 2

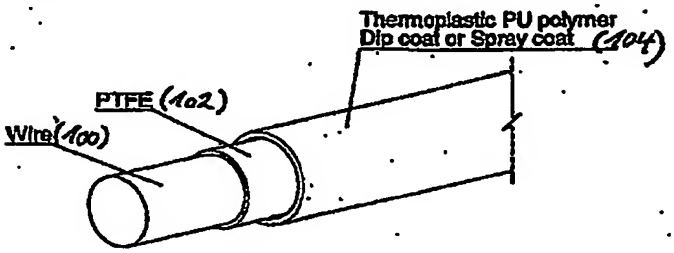


Fig. 3

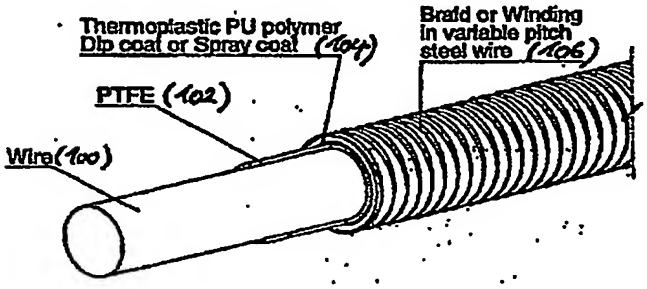
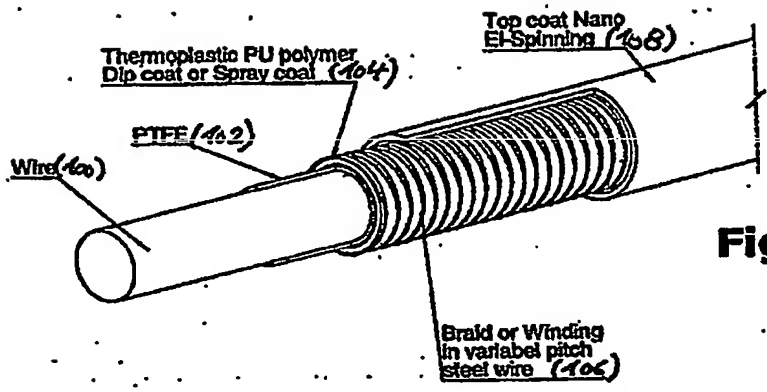


Fig. 4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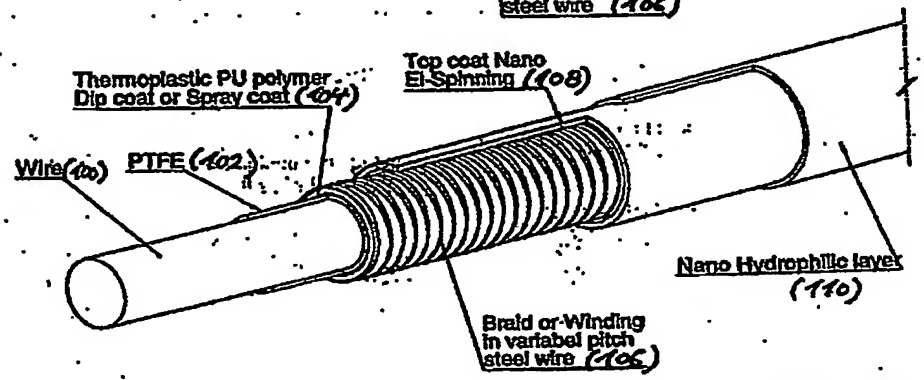
Thermoplastic PU polymer
Dip coat or Spray coat (104)
PTFE (102)
Wire (100)
Braid or Winding
in variabel pitch
steel wire (106)

Fig. 5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steel wire (106)

Fig. 6

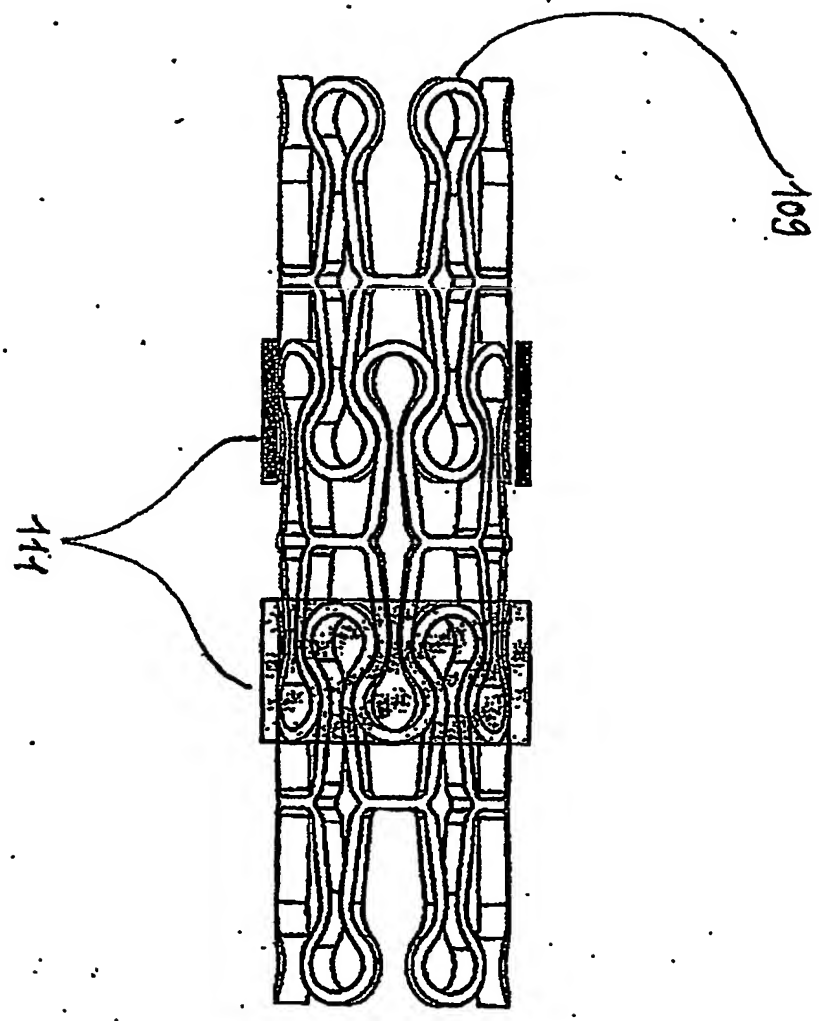

Fig. 7

Fig. 8

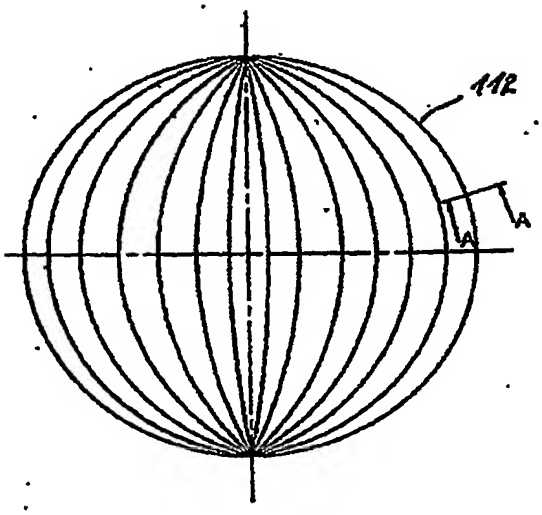

Fig. 9

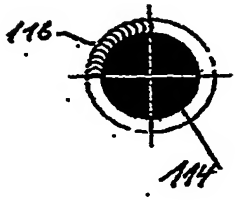

Fig. 10

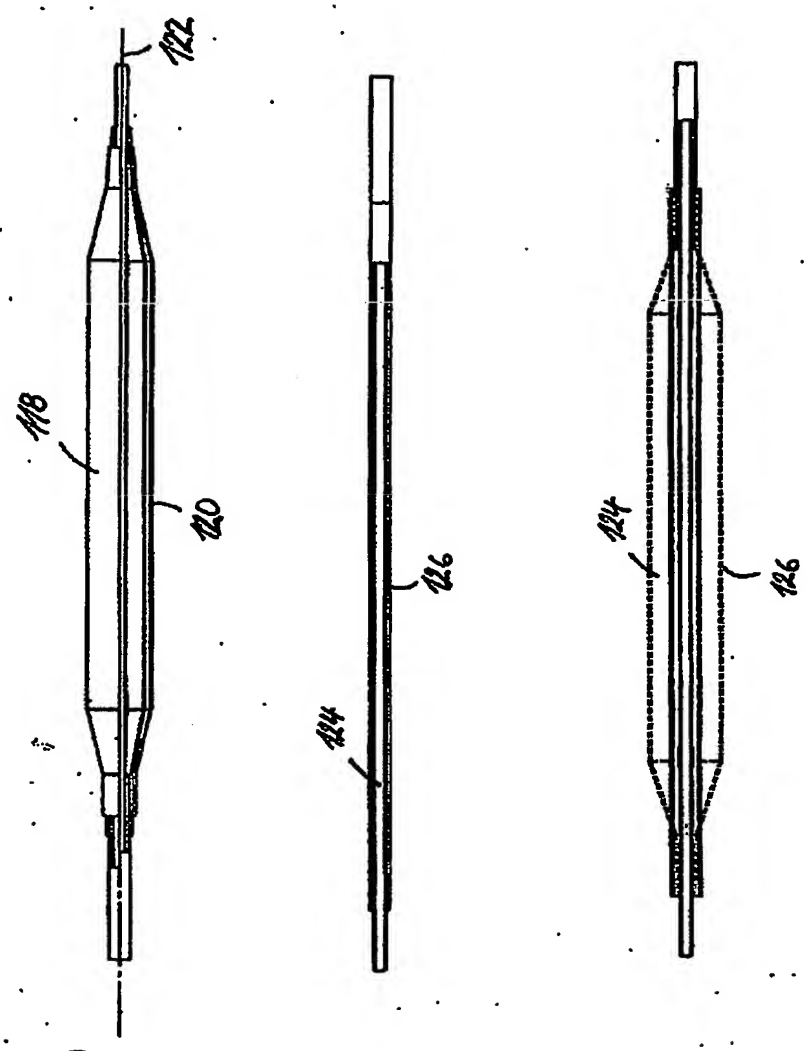

Fig. 11

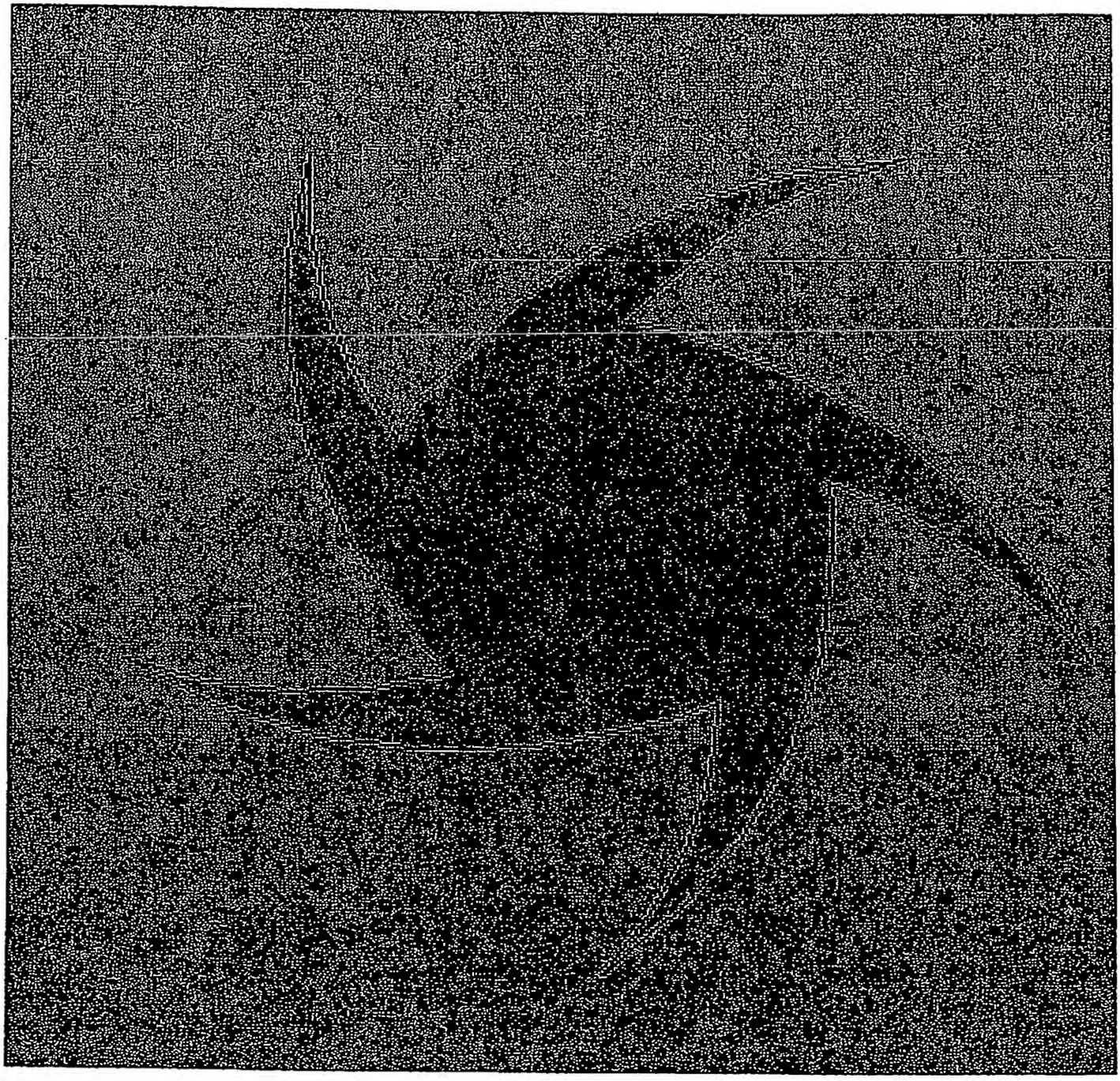

Fig. 12

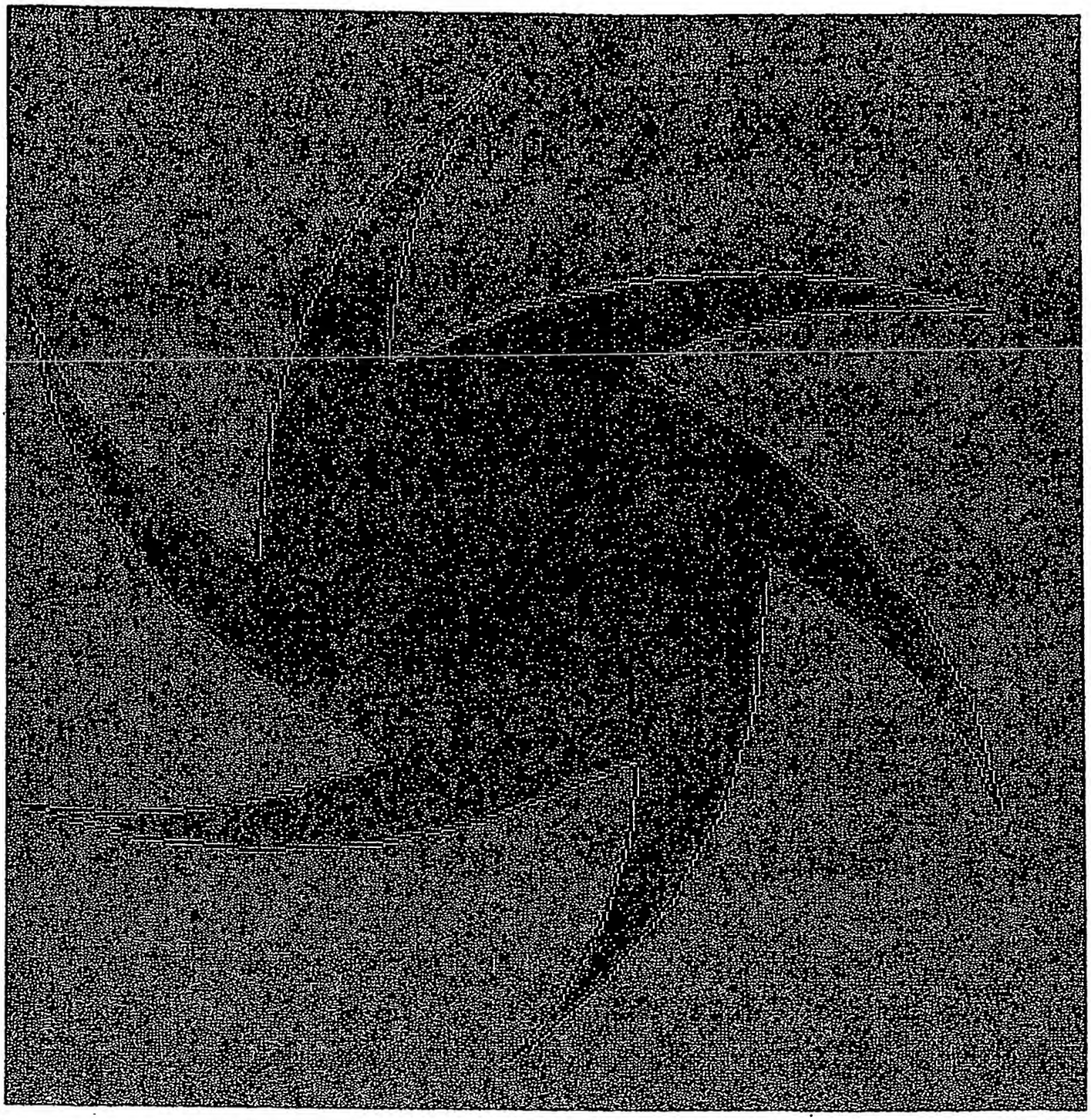

Fig. 13

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